Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-20 are pending in the application, with claim 1 being the sole independent claim. Claims 21 and 22 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Claims 1 and 4 have been amended. Support for the amendment to claim 1 can be found in the specification at pages 11-12, paragraphs 0045 and 0046. Claim 4 has been amended only to add a period at the end of the claim. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Claim Objections

Claims 15-17

The Examiner has objected to claims 15-17 under CFR 1.75 (c) as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Applicants respectfully submit that this objection is improper because each of claims 15, 16 and 17 further limit the transient K^+ current of the previous claim (claim 13) to specific types of transient K^+ currents.

Applicants assert that a transient K^+ current has several discernible subtypes which is supported by information disclosed in the specification, wherein subtypes I_A, I_D and I_{TO} are described. *See* specification, page 12, lines 5-6. Each of these subtypes is specifically defined in the specification. I_A refers to a 4-aminopyridine sensitive, rapidly activating-rapidly inactivating K^+ current present in the neurons of a mammal. *See* specification, page 13, lines 22-23. I_D refers to a rapidly activating-slowly inactivating K^+ current present in the neurons of a mammal. *See* specification, page 14, lines 11-12. I_{TO} refers to a rapidly activating-rapidly inactivating K^+ current present in the cardiac myocytes of a mammal. This particular subtype contributes most significantly to initial depolarization of the cardiac action potential. *See* specification, page 14, lines 23-26.

Moreover, I_A and I_D are distinct and separate transient K^+ currents that appear to exist independently, and play different roles in neurophysiology. This argument is supported by Storm, "Temporal integration by a slowly inactivating K^+ current in hippocampal neurons," *Nature*, *336*: 379-381 (1988), previously submitted in the Information Disclosure Statement filed October 2, 2001. Storm discusses at page 380, left column, second paragraph, the pharmacological block of I_D but not I_A in the presence of low concentration 4-aminopyridine, *i.e.* 4-AP. In this instance, the transient K^+ current affecting the neuron's behavior is attributed to the I_A subtype over the I_D subtype. The present invention concerns the behavior of a neuron as a result of a compound which increases a transient K^+ current. A person of ordinary skill in the art would recognize

that the increased transient K^+ current could be attributed to a single subtype such as I_A or I_D, or a combination of subtypes.

Applicants believe the Examiner's objection to claims 15-17 has been properly traversed, and withdrawal of this objection is respectfully requested.

Claim 4

The Examiner has objected to claim 1 because the claim does not end in a period. Applicant has amended the claim herein to correct this informality. The Examiner's objection to claim 1 has been properly accommodated, and withdrawal of the objection is respectfully requested.

Rejections Under 35 U.S.C. § 112

The Examiner has rejected claims 1-20, in part, by alleging that the specification fails to provide any guidance for practicing the claimed invention outside of magnocellular neurons of the paraventricular nucleus (PVN) of the hypothalamus. The claimed invention is directed to "excitable cells" which include neurons, such as interneurons, sensory neurons and motor neurons, and cardiac myocytes

In response to this rejection, Applicants have amended claim 1 to more clearly define the scope of the invention, encompassing only cells expressing a transient K^+ current. It would not require undue experimentation for a skilled artisan to use the disclosed method in any type of cell expressing a transient K^+ conductance. Presently, it is reported that modulation of 4-AP sensitive transient K^+ conductances of magnocellular

neurons translates into definitive changes in the cell's ability to withstand excitotoxic challenge. *See* specification, page 23, lines 16-17. Furthermore, the present disclosure teaches that transient K^+ conductance plays a dominant role in controlling the excitability of PVN magnocellular neurons, contributing to the resistance of these neurons to excitotoxic cell death. *See* specification, Figure 3. A skilled artisan having read the teachings of the present application would know that such a transient K^+ conductance is a viable target for preventing excitotoxic damage after an ischemic event in any cell expressing a transient K^+ conductance. Moreover, Applicants have recently succeeded in showing that the claimed method will also work in neurons of the nucleus tractus solitarius of the brain. These neurons overexpress transient K^+ conductance. *See* Vincent and Tell, *Eur. J. Neurosci. 8*(12):2748-2752 (1996) submitted in the Supplemental Information Disclosure Statement filed June 11, 2002. These findings support the conclusion that transient K^+ conductances are responsible for protection of multiple cell types from damage due to ischemic events. Furthermore, the existence of transient K^+ currents in diverse cell types is covered in Rogawski. *See* Rogawski, *Trends Neurosci. 8*:214-219 (1985) submitted in the Information Disclosure Statement filed October 2, 2001. The reference states, "[t]he membranes of most excitable cells contain a distinct set of potassium channels that rapidly open and close following depolarization, giving rise to a transient outward membrane current (I_A)." *See* page 214 (abstract), lines 1-3.

The Examiner has also rejected claims 1-20, in part, by alleging that the term "patient" is extremely broad, referring to a mammal, and that there is not enough guidance to be able to predict that the invention would work in all mammals. Applicants

argue that the glutamic excitotoxicity model is one of the best known models for ischemic damage, and a skilled artisan would know that the results of a glutamic excitotoxicity assay can be extrapolated to neurons of different species. Moreover, Applicants respectfully submit that calculating interspecies pharmacokinetic scale-up is routine and predictive of mammalian pharmacology. *See* Mordenti, "Man versus Beast: Pharmacokinetic Scaling in Mammals," *J. Pharm. Sci. 75*:1028-1040 (1986) submitted in the Supplemental Information Disclosure Statement filed June 11, 2002.

The Examiner has also rejected claims 1-20 by alleging that "the amount of compounds, both discovered and not yet discovered, that increase potassium current in neurons is vast." Applicants respectfully traverse this rejection on the ground that with concern to the breadth of a claim relative to enablement, the only relevant concern should be whether the scope of enablement provided to one of ordinary skill in the art by the disclosure is commensurate with the scope of protection sought by the claims. *In re Moore*, 439 F.2d 1232, 1236, 169 USPQ 236, 239 (CCPA 1971). Applicants have shown that a compound, saralasin, provides resistance to glutamate-mediated excitotoxic cell death by means of enhancing the transient K^+ conductance through angiotensin-II inhibition. *See* specification, Figure 4. Thus, the present invention is directed to a method of using transient K^+ conductance modulators to prevent cellular damage during or after an ischemic event. In rejecting claims 1-20 on the basis of the large amount of compounds capable of preventing excitotoxic damage by increasing transient K^+ current , the Examiner is requiring more disclosure than is legally required to enable an invention. The enablement requirement of 35 U.S.C. § 112, first paragraph "requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by

the specification to persons of ordinary skill in the art." *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). To require that Applicants narrow the scope of transient K^+ modulators in the claimed method would not adequately protect the inventors who have discovered a method of preventing damage to the excitable cells of a patient that express a transient K^+ conductance, where the patient undergoes or has undergone an ischemic event, comprising administering a compound which increases a transient K^+ current in said cells. In *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976), the court stated:

> [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

Applicants submit that the claim is no broader than that which the inventors are entitled by statute.

The Examiner also alleges that "there is no evidence of record that would suggest . . . that any given compound that increases neuronal potassium current would be effective in preventing damage to cells affected by an ischemic event." Applicants respectfully traverse this rejection based on the data given in the specification. Specifically, the specification teaches that it had been previously disclosed by a present inventor that 4-aminopyridine, *i.e.* 4-AP, inhibits I_A in magnocellular neurons. *See* Bains and Ferguson, *Eur. J. Neurosci. 10*:1412-21 (1998), previously submitted in the Information Disclosure Statement filed October 2, 2001. Presently, it is reported that the effects of 4-AP sensitive transient K^+ conductance on magnocellular neuron cell

excitability translates into definitive changes in the cell's ability to withstand excitotoxic challenge. *See* specification, page 23, lines 16-17. Furthermore, the present disclosure teaches that transient K^+ conductance plays a dominant role in controlling the excitability of magnocellular neurons, contributing to the resistance of these neurons to excitotoxic cell death. *See* specification, Figure 3. The data in Figure 3 demonstrate that in the presence of angiotensin-II, a known inhibitor of transient K^+ conductance in magnocellular neurons, such neurons are susceptible to excitotoxic injury by a N-methyl-D-aspartate (NMDA) agonist. In the absence of angiotensin-II, no cell death is observed in these neurons in the presence of such a NMDA agonist. The present invention teaches a protective role of transient K^+ conductance in neurons during an excitotoxic insult. Because in the aftermath of an ischemic event, it is the excitotoxic insult that eventually leads to neuronal death, the present inventors have disclosed a method of preventing cellular death by increasing the protective transient K^+ conductance in a cell expressing a transient K^+ conductance. Until this discovery, most research in the area of cerebral ischemic events has involved blood clot dissolvers, glutamate antagonists, Ca^{+2} channel antagonists and calcium-activated K^+ channel antagonists. The present invention is directed to transient transient K^+ conductance modulators. Thus, the present disclosure teaches that transient K^+ conductances are a novel target for therapies directed toward preventing damage to excitable cells expressing K^+ conductance following an ischemic event. It would not require undue experimentation for a person of ordinary skill in the art to practice the invention as claimed to use a compound to target transient K^+ conductance in an excitable cell to prevent excitotoxic damage in said cells in a patient during or after an ischemic event.

The Examiner also has alleged that in view of the working examples one skilled in the art would not conclude that the results of experiments could be extrapolated to practice a method to prevent damage to the excitable cells of a patient during an ischemic event using any compound that increases potassium current. Applicants respectfully disagree. The glutamatic excitotoxicity model employed in the specification is one of the best known models for ischemic damage. Accordingly, a skilled artisan would reasonably expect, based on the data disclosed in the specification in a highly accepted and predictive model, that the claimed method can prevent damage in the excitable cells expressing a transient K^+ conductance following an ischemic event.

The Examiner has further based the above 35 U.S.C. § 112 rejection by alleging that the specification does not teach the guidance to practice the invention with regard to route, duration and quantity of administration of a compound which increases potassium current to a subject. Applicants respectfully traverse this assertion based on the ground that one of ordinary skill in the art would easily determine such parameters once she was aware of the pioneering method claimed in the instant invention. A skilled artisan would recognize that the claimed method involves transient K^+ currents as a novel target in treating and/or preventing ischemic damage to excitable cells, and she would be able to establish the best route, duration, and quantity for a given transient K^+ conductance modulator using the claimed method.

For the reasons cited above, Applicants respectfully request the Examiner to reconsider and withdraw the 35 U.S.C. § 112 rejection.

Other Matters

Applicants note that the Examiner did not consider two of the references previously submitted in the Information Disclosure Statement filed October 2, 2001. On the Examiner-initialed Form PTO-1449 returned to Applicants, the Examiner indicates that References AC1 and AR2 are "not present."

Enclosed please find a copy of the return postcard, date-stamped by the U.S. Patent and Trademark Office as having received, on October 2, 2001, the items listed thereon, including the 49 references cited in the Information Disclosure Statement.

Submitted herewith is a copy of Document AC1 (U.S. Patent No. 5,565,483), Document AR2 (Bains, J.S. and Ferguson, A.V., *NeuroReport 8:*2101-2105 (1997)), and the Form PTO-1449 pages wherein these references are cited. It is respectfully requested that the Examiner initial and return a copy of the enclosed PTO-1449 pages, and indicate in the official file wrapper of this patent application that all the documents cited thereon have been considered.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for

allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

In the Claims:

Claims 21 and 22 have been canceled.

Claim 1 has been amended as follows:

1. (Once amended) A method of preventing damage to the excitable cells of a patient <u>that express a transient potassium (K^+) conductance</u> which comprises administering to said patient during or after said patient undergoes or has undergone an ischemic event, an effective amount of a compound which increases a transient potassium (K^+) current in [the] <u>said</u> excitable cells of said patient.

Claim 4 has been amended as follows:

4. (Once amended) The method of preventing damage to the excitable cells of a patient as claimed in claim 1, wherein said transient K^+ current is I_A.